REMARKS

Claims 1-21 are pending in this application. Claims 13-20 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1-12 are under examination. Claim 21 has been added to more clearly describe the claimed invention. No new matter is believed added. Support for the added new claim can be found throughout the specification as filed, but more specifically in Examples 5-6 and 8-9 (on pages 18-23), wherein dairy cattle were protected from *M. bovis* mastitis by systemic administration of the vaccine.

In light of the following remarks, Applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

I. Rejections under 35 U.S.C.§ 112, first paragraph

Claims 1-12 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the Office Action alleges that claims 1-12, drawn to a vaccine composition containing at least one inactivated or attenuated *M. bovis* biotypes selected from the group consisting of biotype A, biotype B and biotype C, are not enabled because cell lines with the required properties are not known and are not publicly available, the cell lines can not be reproducibly isolated from nature without undue experimentation and, therefore, inventions using these cell lines require the use of a suitable deposit in order to be enabled.

Applicants respectfully disagree with the Examiner's assertions regarding the lack of enablement in the absence of a deposit.

Specifically, the Office Action's assertion that the invention is not enabled because the cell lines with the required properties are allegedly not known and allegedly cannot be isolated without undue experimentation is incorrect. As filed, the specification teaches the isolation of *M. bovis*, the culture of the isolated *M. bovis*, its manipulation to produce isolated biotypes and the identification of the isolated biotypes (see Example 1, pages 11-14 and Example 2, parts A & B, pages 14-16). The collection and manipulation of samples to generate the specific embodiments of the present invention as disclosed in the examples, or the same manipulation of other samples, does not rise to the level of undue experimentation. As is summarized in *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977) (MPEP 2164.06), "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In this particular case, the guidance provided includes the steps required to isolate, manipulate, and characterize the isolated biotypes and then to use these isolated biotypes to produce the claimed vaccine. As such, the present application is adequate to fully enable one of skill in the art to make and practice the invention.

Further, Applicants clearly contemplated in the application as filed the production of vaccines in response to newly emergent or newly identified isolates of *M. bovis* (page 6, lines 1-11). Thus, there can be no deposit of all cell lines (biotypes) which are encompassed by the invention as claimed since many of the claimed vaccines include biotypes that are yet to be discovered. However, even as it applies to the biotypes specifically described in the examples of the present application, Applicants submit that the Examiner's assertion that exact replication of the *M. bovis* cultures described is an unpredictable result is irrelevant to a finding that the present invention is fully enabled. Rather, Applicants submit it is only necessary that one of skill in the art be able to use the present disclosure to isolate either a *M. bovis* culture or a collection of different *M. bovis* cultures with the same biotype. The culture or collection of cultures need not be the identical culture it rather need only be a culture or collection of cultures of the same biotype. This is not unpredictable, nor is it a task requiring undue experimentation. The

presently disclosed and claimed biotypes are not rare strains of *M. bovis* found only in some faraway and isolated location, rather, they are the commonly encountered biotypes of a far too common disease afflicting cattle herds throughout the United States which cause significant economic damage. The very fact that these biotypes of *M. bovis* cause significant damage throughout many regions of the United States, is a strong indication that they can be readily isolated, cultured and identified using the techniques disclosed in the present application. Correspondingly, Applicants submit that any requirement that a biological deposit be made for the purpose of enabling the practice of the invention is unfounded. Applicants request removal of this ground of rejection and allowance of all pending claims to issue.

II. Rejection under 35 U.S.C. § 102

Claims 1-4 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Howard et al. Specifically, the Office Action alleges that claims 1-4 drawn to a vaccine composition comprising at least one inactivated or attenuated *M. bovis* biotype and a pharmacologically acceptable excipient are anticipated by a quadrivalent vaccine containing, *inter alia*, killed antigens of *M. bovis*. Further distinctions between what is disclosed by Howard et al. and the present application are indicated as inherent in the vaccines of the prior art. Further, the Examiner emphasizes that it is the Applicants' burden to show a novel or unobvious difference between the claimed product and the prior art.

In response, Applicants submit that Howard et al. does not anticipate the present invention as recited in any of the claims as filed, but even more clearly, does not anticipate the invention as recited in newly added claim 21.

Howard et al., in the abstract, describes the use of two vaccines. One is a quadrivalent vaccine containing antigens of respiratory syncytial virus (RSV), parainfluenza virus type 3, *M.*

bovis and *M. dispar*. The other is a monovalent vaccine containing antigens from RSV only. In the trials testing these vaccines, there was purportedly a significant protective effect from both the quadrivalent and monovalent vaccines. While unvaccinated calves, the control group, suffered a death rate of 9% from pneumonia, those vaccinated with the quadrivalent or monovalent vaccines suffered a death rate of only 2% or 3%, respectively. Further, the proportion of calves experiencing respiratory disease was 38% in the control group, 25% in the quadrivalent vaccine group and 27% in the monovalent (i.e., RSV-only) vaccine group (see abstract). The monovalent vaccine, which does not contain *M. bovis* antigens, shows a near identical protective effect against either death or the more nebulously defined respiratory disease as the quadrivalent vaccine which does contain *M. bovis* antigens. With these facts, as described in the abstract, there is no clear teaching of a vaccine protective against *M. bovis* clinical disease.

Indeed, even elsewhere in Howard et al. where the results in batch 85/1 are described, the authors state that "*M. dispar* may have been a component of disease in batch 85/1, interacting with respiratory syncytial virus. The slightly higher degree of protection would appear to support this view but the numbers were too small to draw a firm conclusion" (Howard et al., first full paragraph on page 375). In this statement describing the best evidence in Howard et al., Howard et al., admit that the results they report are insufficient to conclude that there was a vaccine effect for *M. bovis*. Thus, there is insufficient evidence in Howard et al. to conclude that there was any protective effect of the quadrivalent vaccine against *M. bovis* clinical disease, and an inadequate basis to sustain a finding of anticipation. Even "(w)hen the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same," and when "the applicant has the burden of showing that they are not," *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990), the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily have the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. As the "best evidence" for any effectiveness of the quadrivalent vaccine in the cited reference includes alternative explanations, presented by the

authors, and a clear admission that the numbers were too small to draw firm conclusions, Applicants submit that Howard et al. itself teaches that the prior art product does not necessarily have the characteristic of the claimed product, namely, a protective effect against *M. bovis* clinical disease. Thus, Howard et al. does not anticipate the present claims. Applicants request withdrawal of this ground of rejection.

Further, Applicants submit that newly added claim 21, directed to vaccines protective against *M. bovis* mastitis, are clearly not anticipated by the vaccine of Howard et al., which is only alleged to be protective against respiratory infection and not other types of *M. bovis* disease. The present vaccine provides the first actual protection against mastitis, a particularly problematic clinical manifestation of *M. bovis* infection that results in inflamed and swollen udders and causes significant losses in milk production and in lower milk quality. Thus, by providing protection against mastitis, the present invention provides a significant improvement over any previous *M. bovis* vaccine including any putative vaccine effect of the composition of Howard et al. or of any other.

The novelty of the present invention which is protective against mastitis, is evidenced by the recognition by those of skill in the art that vaccines available prior to the present invention, including those of Howard et al., are unsuitable and lack effectiveness. This lack of efficacy is reflected in the persistent practices indicated to prevent the spread and to mitigate the effects of the disease. Specifically, because no previously available "vaccine" was able to prevent the transmission of the disease or the losses associated with *M. bovis* mastitis, the identification and culling of infected cows is indicated as necessary. For example, in Heller et al., *Vet. Microbiol.* 37: 127-133 (1993) (Attachment 1), it is stated on page 127 that "[t]o control the spread of this disease an early detection of the pathogen is crucial since the removal and culling of infected cows is necessary to prevent fresh infections." Further, in a recent two-part series on *Mycoplasma* mastitis (*Bovine Veterinarian*, pp. 4-8, Sept., 2001 (Attachment 2) and *Bovine*

Veterinarian, pp. 12-20, Oct., 2001 (Attachment 3)), methods and practices to both prevent the spread of the disease and to mitigate its effects are detailed. The listed methods and practices do not include vaccination, because no effective vaccine for the prevention of *Mycoplasma* mastitis is known in the art.

In the absence of any disclosure in the literature of an effective vaccine for the prevention of *M. bovis* mastitis, Applicants submit that the present vaccine as presented in newly added claim 21 is novel and non-obvious. Therefore, Applicants request allowance of this claim to issue.

III. Rejection under 35 U.S.C. § 103

Claims 5-12 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Howard et al. and in view of Poumarat et al. Specifically, the Office Action alleges that claims 5-12 drawn to the vaccine composition of claim 1, wherein the *M. bovis* bacteria is selected from a group consisting of biotype A, biotype B, biotype C and combinations thereof, is obvious in light of Howard et al. which allegedly teaches vaccines containing *M. bovis* antigens and Poumarat et al. which allegedly teaches the identification of biotypes by use of restriction endonuclease cleavage and gel electrophoresis. Correspondingly, it is alleged that it would have been *prima facie* obvious to one of ordinary skill in the art to add the *M. bovis* isolates of Poumarat et al. to a vaccine composition according to Howard et al.

Applicants submit that no combination of references, including Poumarat et al. with Howard et al., properly establish a *prima facie* case of obviousness of this invention. Specifically, the three basic criteria of a *prima facie* case of obviousness, namely; (1) some suggestion or motivation to combine reference teachings; (2) a reasonable expectation of success; and (3) the combination of references must teach or suggest all claim limitations, can not be met by a combination including Howard et al. Because Howard et al. does not provide a

vaccine protective against *M. bovis* clinical disease in general, or more particularly, against *M. bovis* mastitis, there is no motivation to modify Howard et al. There is no teaching within either Howard et al. or Poumarat et al. to modify a vaccine by inclusion of different or multiple biotypes. Furthermore, there is no reasonable expectation that a combination of the teaching of Howard et al. and Poumarat et al. would produce a vaccine against *M. bovis* clinical disease.

It is also important to understand the distinction between a serological response which is indicative of infection and an immune response which is able to confer a protective resistance against infection. Serological responses that result in measurable immunological activity, but provide little or no effective protective benefit, are not uncommon. As is indicated in Howard et al. (Table 2, page 373), inoculation with the quadrivalent vaccine resulted in a serological response in 100% of the calves when challenged with *M. bovis*. In light of this clear response, and the continued inability of the vaccine to provide any clear protection against clinical disease (as outlined above), there would be no motivation to use any number of Poumarat et al.'s isolates to generate other vaccines. The knowledge of those of skill in the art at the time of the present invention indicates that the presence of serum antibody does not confer immunity; "[n]o simple relationship was established between serum antibody (SRH) and immunity. As found previously with the complement fixation test (Howard et al., 1977a), animals inoculated by the M/M system, which were not resistant, had similar levels of SRH antibody in their sera to animals inoculated by the M/T regime which were resistant" (Howard et al., *Research in Veterinary Science* 28: 242-249 (1979), provided as Attachment 4, starting last paragraph of page 247). It should also be noted that "resistant," as used in Howard et al. (1979), does not necessarily indicate immunity or protection from *M. bovis* disease. As outlined in Howard et al. (1979), "resistance was measured by determining the effect of various treatments on the number of *M. bovis* isolated from the lungs three weeks after intratracheal challenge." There is no actual determination that the vaccination protocols used resulted in protection from *M. bovis* disease.

Thus, the present highly successful vaccine would not have been obvious to the skilled person based on Howard et al. and Poumarat et al.

The failure of prior art vaccines to protect against M. bovis disease has also been demonstrated for *M. bovis* mastitis. In studies using a prior vaccine comprising adjuvanted, inactivated *M. bovis*, vaccination was unable to prevent mastitis (e.g., Boothby et al., *Can. J. Vet. Res.* 50: 200-204 (1986); provided as Attachment 5). In that particular study, cows were inoculated three times subcutaneously and then twice by an intramammary infusion. Both vaccinated and unvaccinated cows were then challenged with *M. bovis* by intra-mammary exposure. Vaccinated cows were not protected from acute infection. Further, the vaccinated cows suffered significant and persistent reductions in the level of milk production, whereas the unvaccinated cows suffered a less significant and more transient drop in milk production (Attachment 5; Figure 2). The significant drop in milk production observed in vaccinated cows was, like in unvaccinated cows, also "...accompanied by abnormal and sometimes purulent lacteal secretions" (Attachment 5; page 203). Thus, the disclosed vaccine was neither protective against *M. bovis* mastitis, a *M. bovis* clinical disease, nor was it useful for reducing the losses associated with *M. bovis* mastitis. Thus, even more clearly, the knowledge of those of skill in the art teaches against the combination of any reference teaching *M. bovis* vaccines for preventing mastitis as prior vaccines were known to cause significant side-effects and to not be protective.

As Howard et al. and Poumarat et al. do not fulfill even one of the three criteria which must be met in order to properly establish a prima facie case of obviousness, Applicants request withdrawal of this basis of rejection.

Pursuant to the above amendments and remarks, consideration and allowance of the pending application is believed warranted. The Examiner is invited and encouraged to directly

contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A fee in the amount of $200.00 for a two month extension of time (small entity) is to be charged to a credit card and such payment is authorized by the signed, enclosed document entitled: Credit Card Payment Form PTO 2038, however, the Commissioner is hereby authorized to charge any additional fees which may be required to Deposit Account No. 14-062.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on the date shown below.

Gwendolyn D. Spratt — 3-11-02

Gwendolyn D. Spratt — Date